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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/695,509	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-22,24,26-29,31 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22, 24, 26-29, 31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 8/11/2008 in response to the previous Non-Final Office Action (4/10/2008) is acknowledged and has been entered. It is important to note that, the recitation of "vitamin D" in the 7th line of claim 20 and 27 appears to be a limitation which has been added in the current amendment, but has not be underlined, e.g., showing that it was added. For examination purposes, such recitation has been interpreted as being part of the amendment.

Claims 20-22, 24, 26-29, 31 and 33 are currently pending and under consideration.

The Declaration Under CFR 1.132 filed on 8/11/2008 by the inventor, Gary G Schwartz is sufficient to overcome the rejection of Claims 20-22, 24, 26-29, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Getzenberg et al. (Urology 1997; 50: 999-1006, of record) in view of Haussler et al. (JAMA 1982; 247: 841-844, *of record*) based upon the showing that there is no reasonable expectation of success that substitution of 25-hydroxyvitamin D for 1,25 dihydroxyvitamin D would be effective at inhibiting tumor growth.

Rejections withdrawn:

The rejection of Claims 20-22, 24, 26-29, 31 and 33 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants amendments.

The rejection of Claims 20-22, 24, 26-29, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Getzenberg et al. (Urology 1997; 50: 999-1006, of record) in view of Haussler et al. (JAMA 1982; 247: 841-844, *of record*) is withdrawn in view of Applicants arguments and the Declaration Under CFR 1.132 filed on 8/11/2008 by the inventor, Gary G Schwartz.

New Rejections upon Reconsideration:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-22, 24, 26-29, 31 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "effective amount" in claims 20 and 27 is a relative phrase which renders the claim indefinite. The phrase "effective amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the instant case, an effective amount of 25-hydroxyvitamin D or an analog, salt or derivative thereof appears to be essential for one of skill in the art to practice the claimed invention. However, while the claims encompass inhibiting tumor growth, it is unclear whether the inhibition of tumor growth is the function achieved by administration of an effective amount or whether the accumulation of 25 to about 250 nmol of the compound in the target-organ is the function achieved by the administration of the effective amount. For example, the specification teaches that "an effective amount of 25 (OH)D administered into the target organ would be any amount which, when administered, increases local cellular levels of 25(OH)D, but maintains serum levels of 25(OH)D within this "normal" range (page 18, lines 1-14). Alternatively, the specification teaches that an alternative determination of an effective amount of 25(OH)D administered in accordance with the method of the subject invention is to administer an amount which raises the level of 25(OH)D toward the high end of its normal range in the target organ, but which does not raise systemic 1,25(OH2)D above the high end of its normal range (Page 18, lines 15-24). Thus, the specification appears to suggest that the "effective amount" refers to the level of 25(OH)D in the target organ and not inhibiting tumor growth. Thus, an effective amount of 25-hydroxyvitamin D or an analog, salt or derivative thereof will be interpreted as an amount effective to increase 25(OH)D in the target organ.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-22, 24, 26-29, 31 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Claims 20 and 27 were amended on 1/14/2008 to include the limitation of "and results in intra-target organ levels of said 1,25-dihydroxyvitamin D between about 25 and about 250 nmol/L". However, a careful review of the specification and claims, as originally field, does not appear to provide support for this limitation. For example, the claim 6, as originally filed, recites "wherein the effective amount of said metabolic precursor is an amount which results in intra-target organ levels of said metabolic precursor between about 25 and about 250 nmol/L". Moreover, the specification (page 18) when discussing target organ concentration teaches:

> The normally observed concentration of 25(OH)D in serum is about 20- 150 nmol/L (8-60 ng/ml). However, circulating concentrations of" up to 250 nmol/L (100 ng/ml) 25(OH)D have commonly been observed in lifeguards after a full summer of exposure to sunlight and is considered to be normal (Holick, M.F., .1. *Nutrition, Suppl. 120:1464-1469* (1990)). Concentrations of about 350 nmol/L or more are considered to be dangerous to the health of the individual. Hypovitaminosis D, i.e., a deficiency in serum 25(OH)D, is a condition defined when serum levels fall below about 25 nmol/L (10 ng/ml). Thus, an effective amount of" 25(OH)D administered into the target organ would be any amount which, when administered, increases local cellular levels of 25(OH)D, but maintains serum levels of 25(OH)D within this "normal" range. Preferably, 25(OH)D levels are increased in the target organ substantially above 25 nmol/L but less than 250 nmol/L. More preferably, 25(OH)D levels are increased to between about 50 and 150 nmol/L.
>
> Normal serum levels of 1,25(OH)2D range between about 38-144 pmol/L (16-60 pg/ml). Thus, an alternative determination of an effective amount of 25(OH)D administered in accordance with the method of the subject invention is to administer an amount which raises the level of 25(OH)D toward the high end of its normal range in the target organ, but which does not raise systemic 1,25(OH)2D above the high end of its normal range. For example, 25(OH)D levels preferably can be raised to increase intra-organ levels to between about 25 and 150 nmol/L, but where systemic 1,25(OH)2D levels remain less than 145 pmol/L. More preferably, 1,25(OH)2D levels remain below 125 nmol/L when 25(OH)D is administered to a target cell, organ, or tissue.

Thus, while the specification and claims, as originally filed, appear to teach concentrations of 25 (OH)D, e.g., a metabolic precursor of 1,25-dihydroxyvitamin D, the specification only appears to discuss concentrations of 1,25-dihydroxyvitaminD systemically and not within the target organ. Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06

Claims 20, 22, 24, 26-27, 29, 31 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims recite a method for inhibiting tumor cells, ... comprising the step of administering to a patient a composition comprising an effective amount of 25-hydroxyvitamin D, or an analog, salt or derivative thereof capable of being hydroxylated by vitamin D 1-alpha hydroxylase in a target organ ... and results in intra-target organ cell levels of said 1, 25-dihydroxyvitamin D between about 25 and about 120 nmol/L. Thus, the claims broadly encompass a genus of analogs or derivates of 25-hydroxyvitamin D which are hydroxylated in the 1 position by 1-alpha hydroxylase resulting in intra-target organ levels of 1,25-dihydroxyvitamin D between about 25 and about 250 nmol/L. However, the written description in this case only sets forth 25-hydroxyvitamin D which is converted to 1,25-dihydroxyvitamin D by 1-alpha hydroxylase thereby resulting in intra-target organ cell levels of said 1,25-dihydroxyvitamin D between 25 and about 250 nmol/L.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The specification teaches (page 17, lines 10-21) that one aspect on the invention is to administer an effective amount of a vitamin D metabolite which can be metabolically converted by the target cells by 1,25(OH)2D, wherein the vitamin D metabolite does not cause an increased risk of skin cancer (as compared to sun or ultraviolet (UV) ray exposure), vitamin D toxicity (as compared to supplemental excessive vitamin D administration, and does not significantly contribute to hypercalcemia (as compare to administering 1,25 (OH)2D). The specification further teaches

Page 17, lines 21-22) that the preferred embodiment is an effective amount of 25 (OH)D, or an analog, derivative, salt, or functional equivalent thereof. With regards to the analogs or derivatives of 25(OH)D, the specification teaches that analogs and derivatives of 25(OH)D include, but are not limited to, alkylated, glycosylated, arylated, halogenated, or hydroxylated 25(OH)D, orthoesters of 25 (OH)D, wherein the vitamin D analogs can be obtained following the methods disclosed in a plethora of US. Patents (page 18, lines 25+). With regards to the "functional equivalent", the specification teaches that the term "functional equivalent" refers to any compound which can be used as a substrate for 1a-Ohase or other wise be converted to 1,25(OH)2D or converted to a compound which can bind to or activate the 1,25 (OH)2D receptor (VDR) (page 19, lines 10-16. Thus, while the specification contemplates any vitamin D metabolite and any derivative, analog or functional equivalent of 25-(OH)D, e.g., 25-hydroxyvitamin D, the specification only reasonably conveys one species of metabolic precursors of 1,25-dihydroxyvitamin D, wherein the metabolic precursor is 25-hydrovitamin D. In other words, the specification appears to be silent on any other analog or derivative of 25-hydroxyvitamin D which can be converted to 1,25-dihydroxyvitamin D. A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description

requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of metabolic precursors of 1,25-dihydroxyvitamin D that encompass the genus nor does it provide a description of structural features that are common to the precursors. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one species is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of metabolic precursors of 1,25-dihydroxyvitamin D, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only 25-hydroxyvitamin D which is converted to 1,25-dihydroxyvitamin D by 1-alpha hydroxylase thereby resulting in intra-target organ cell levels of said 1,25-dihydroxyvitamin D between 25 and about 250 nmol/L, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 20-22, 24, 26-29, 31 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where

no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

Claims 20-22, 24, 26-29, 31 and 33 are drawn to a method of inhibiting tumor cells comprising administering an effective amount of 25-hydroxyvitamin D or an analog, salt or derivative thereof. As such, the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of inhibiting tumors cells, while reducing the risk of UV radiation exposure or vitamin D toxicity, said tumor cells being prostate cancer cells, breast cancer cells, skin cancer cells, pancreatic cancer cells, colon cancer cells, pancreastic cancer cells or lung cancer cells, said method comprising administering to a patient an effective amount of 25-

hydroxyvitamin D or an analog, salt, or derivative thereof capable of being hydroxylated by vitamin D 1-alpha hydroxylase in a target organ to increase levels of a metabolite of said 25-hydroxyvitamin D or its said analog, salt or derivative in said tumor cells in a target organ wherein the tumor cells have a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitamin D from said 25-hydroxyvitamin D and results in intra-target organ cell levels of said 1,25-dihydroxyvitamin D between 25 and about 250 nmol/L. Thus, the breadth of the claims appear to suggest that the administration of an effective amount of a 25-hydroxyvitamin D or an analog, salt, or derivative thereof capable of being hydroxylated by vitamin D 1-alpha hydroxylase in a target organ to increase levels of a metabolite of said 25-hydroxyvitamin D or its said analog, salt or derivative in said tumor cells in a target organ, wherein the tumor cells have a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitamin D from said 25-hydroxyvitamin D and results in intra-target organ cell levels of said 1,25-dihydroxyvitamin D between 25 and about 250 nmol/L is effective for the inhibition of tumor cell growth. In other words, the breadth of the claims appears to suggest that the increased level of the metabolite and not the compound administered has the inhibiting effect.

Guidance in the specification and Working Examples

The specification teaches that one aspect of the invention comprises increasing the local cellular levels of $1,25(OH)_2D$ by administering an effective amount of a Vitamin D metabolite which can be metabolically converted by the target cells to $1,25(OH)_2D$ for the prevention or treatment of cell proliferation, invasiveness, or metastasis (page 17, lines 10-15). With regards to the effective amount, the specification teaches that an effective amount of 25 (OH)D administered into the target organ would be any amount which, when administered, increases local cellular levels of 25(OH)D, but maintains serum levels of 25(OH)D within this "normal" range, wherein normal range is a concentration of 25OHD in serum about 20-150 nmol/L (page 18, lines 1-14). Alternatively, the specification teaches that an alternative determination of an effective amount of 25(OH)D administered in accordance with the method of the subject invention is to administer an amount which raises the level of 25(OH)D toward the high end of its normal range in the target organ, but which does not raise systemic 1,25(OH2)D above the high end of its normal range, wherein the normal serum levels of 1,25 (OH2)D range between about 38-144pmol/L (Page 18, lines 15-24). For example, the speciation teaches that the subject method of administering a metabolic precursor

of 1,25$(OH)_2$D to a patient has been shown to be successful in producing 1,25$(OH)_2$D by prostatic cancer cells and two primary culture of cells, NP96-5 and BPH96-11 (page 19, lines 21+). Moreover, the specification teaches that colon or breast cells have also been shown to possess 1α-OHase activity (page 25, lines 1-2). The specification further teaches that in one embodiment, a polynucleotide construct containing a gene that codes for 1a-OHase can be used to treat a cell exhibiting benign prostatic hyperplasia. Thus, while the specification contemplates what the effective amount of 25-hydroxyvitamin D should be within the target organ relative to normal concentrations and dangerous concentrations, the specification appears to be silent on a correlation between the "amount" of 25-hydroxyvitamin D" needed to increase 1,25-dihydroxyvitamin D in the target cell and inhibition of tumor growth. In other words, the specification appears to be concerned with administering an amount of 25-hydroxyvitamin D within the normal range, but is silent on the conversion of 25-hydroxyvitmain D to 1,25-hydroxyvitamin D in the target cell and the result being effective at inhibiting tumor growth. Similarly, while the specification teaches that prostatic cancer cells and two primary culture of cells, NP96-5 and BPH96-11 successfully produce 1,25 dihydroxyvitamin D from 25-hydroxyvitamin D, the specification appears to be silent on the inhibition of the in vitro cells or whether such as conversion is feasable in vivo and have the desired effect, e.g, inhibition of tumor growth. Lastly, as noted above, while the specification provides a number of examples of converting 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D, the specification appears to be silent on any other analog or derivative of 25-hydroxyvitamin D and the resulting metabolite produced being effective at inhibiting tumor growth.

Quantity of experimentation

The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that vitamin D3 undergoes hydroxylation first in the liver to form 25-hydroxyvitamin D3 which is further hydroxylated in the kidney by Vitamin D 1a-hydroxylse to create the biologically active form 1,25 $(OH)_2$D3 (Ma et al. Molecular and Cellualr Endocrinology 2004; 221: 67-74, of record). With regards to 1,25 $(OH)_2$D3, Ma et al. teach that 1,25 $(OH)_2$D3 has been shown to inhibit established prostatic cancer cell lines as well as primary culture of normal and malignant prostatic epithelial cells (page 67, 2nd column last paragraph to page 68, 1st column). Despite the anti-tumor activity of 1,25 $(OH)_2$D3, Ma et al. teach that systemic hypercalcemia resulting from excessive circulation of 1,25 $(OH)_2$D3 has limited its therapeutic potential and has led investigators to propose new strategies to harness the anti-tumor activity of 1,25 (OH)2D3 while circumventing hypercalcemic activity. For example, Ma et al. teach that this discovery has raised the possibility of intra-prostatic conversion of 25(OH)D3 to 1,25(OH)2D3 by endogenous 1a(OH)ase, allowing the use of the less hypercalcermic 25(OH)D3 instead of 1,25(OH)2D3 as a therapeutic approach (page 68, 1st column, 2nd paragraph). However, Ma et al. teach that 1a(OH)ase activity in human prostate cancer cells is dramatically reduced in comparison to cells derived from normal of benign prostatic hyperplasia (page 68, 1st column, 2nd paragraph). Similarly, Hsu et al. (Cancer Research 2001; 61: 2852-2856, of record) quantified the levels of endogenous 1a-hydroxylase activity in a series of primary cultures of human prostatic epithelial cells derived from normal tissue, BPH, adenocarcinomas and several prostatic CA cell lines (page 2852, 2nd column, 3rd paragraph). Specifically, Hsu et al. found that CA cells had approximately 10 to 20 fold lower levels of 1 a-hydroxylase activity compared with cells from normal tissues (page 2852, 2nd column, 3rd paragraph). Likewise, Whitlatch et al. (J. Steroid Biochem. Molecular Biology 2002; 81: 135-140, of record) compared the levels of 1a-OHase activity in prostate cancer cell lines, LNCaP, DU145 and PC-3 and in primary cultures of normal, cancerous and benign prostatic hyperplasia (BPH) prostate cells (abstract). In particular, Whitlatch et al. observed that compared to primary cultures of normal prostate cells, primary cultures of prostate cancer cells and prostate cancer cell lines demonstrate a marked decline in 1a-OHase activity (page 138, 2nd column, last paragraph and page 137, Figure 1). As such, both Hsu et al. and Ma et al teach

that the proposed strategy of using 25(OH)D3 as a therapeutic agent for prostate cancer will be ineffective (abstract or Hsu et al. and page 68, 1st column, 1st full paragraph of Ma et al.)

With regards to the unpredictability in the art, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4, of record) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320, of record) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. In addition, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Moreover, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042, of record) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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